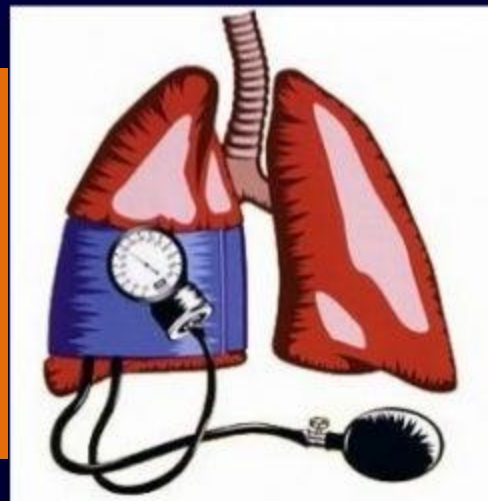
PULMONARY HYPERTENSION

D/AMAT



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- Definition
- Classification of PH
- Pathology & Pathophysiology
- Approach to diagnosis
- Treatment
- Follow-up.

Definition of PAH by WHO

- Increase in blood pressure in pulmonary circulation (either in the arteries, or both in arteries and veins)
- Normal pressure is 14-18mmHg at rest.
- 20-25mmHg on exercise.
- Hemodynamically it is defined as an increase in mean pulmonary arterial pressure to >-25mmHg at rest.
- Can be measured by right heart catheterization.

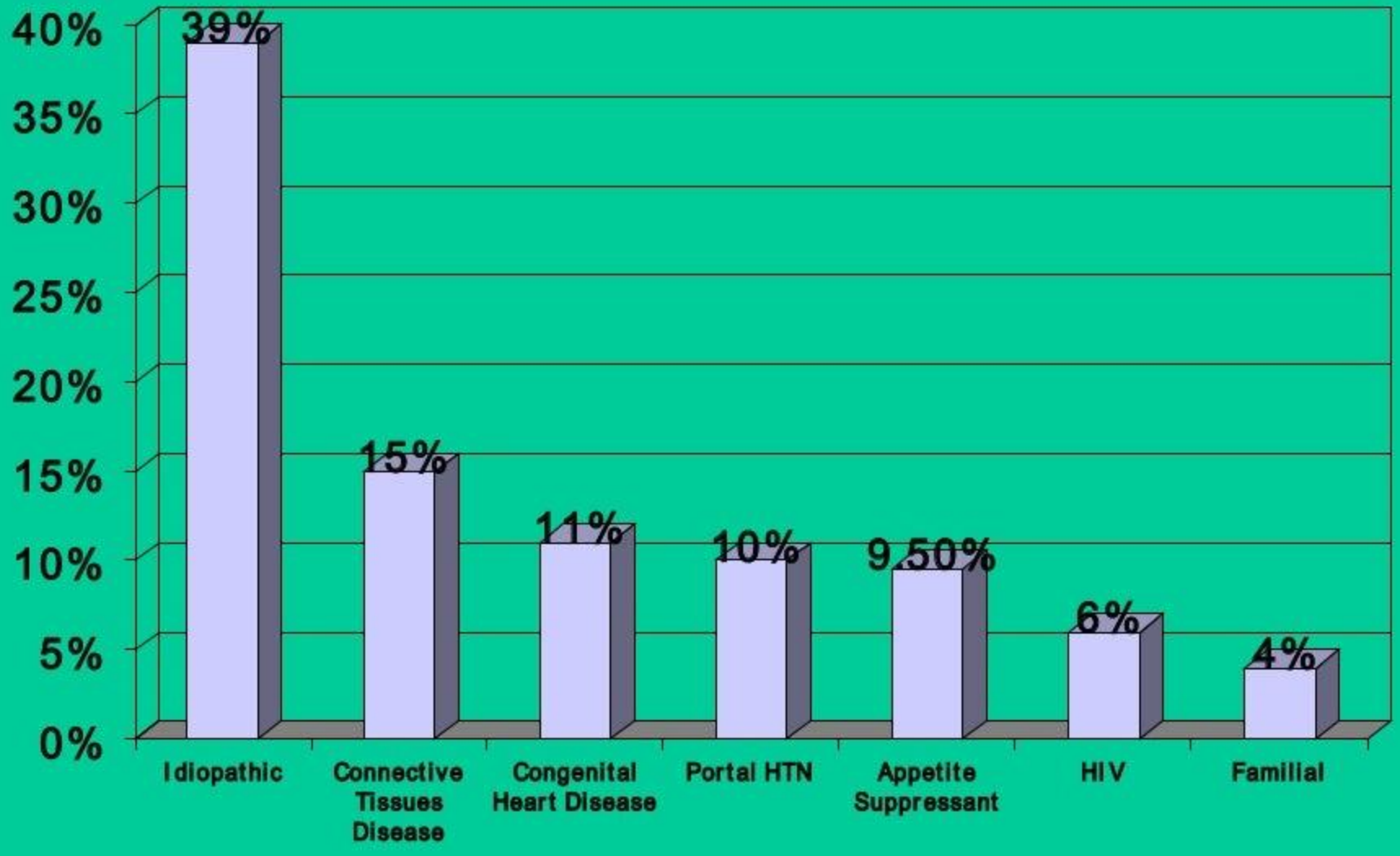
- Two definitions of PH that were previously accepted are no longer used.
- Mean pulmonary artery pressure >30 mmHg with exercise (measured by right heart catheterization)
- Estimated systolic pulmonary artery pressure >40 mmHg (estimated by Doppler echocardiography)

WHO Classifications of Pulmonary Hypertension

1. Pulmonary Arterial Hypertension
2. Pulmonary Hypertension owing to left heart disease
3. PH Secondary to Chronic Hypoxemia
4. Chronic Thrombo-Embolic Pulmonary Hypertension (CTEPH)
5. Miscellaneous (usually extrinsic compression of pulmonary arteries)

WHO Venice 2003 – Later updated in 2008 (Dana point)

Epidemiology of PH



- Obstructive sleep apnea (OSA) – A review of eight studies estimated that the prevalence of mild PH is 15 to 20 % among patients with OSA (*Cardiovascular effects of obstructive sleep apnea –up to date)*

Group 1 - PAH

- IPAH
- Familial – BMPR2, ALK 1,Unknown
- Associated with PAH
  - Connective Tissue Disease (Scleroderma, SLE, MCTD, RA)
  - Congenital Heart Disease
  - Portal hypertension (5-7% of patients)
  - HIV (0.5% of patients)
  - Drugs/toxins (aminorex-, dexfenfluramine-, or fenfluramine-containing products, cocaine, methamphetamine)
  - Other:

  hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders, splenectomy
- Associated with venous/capillary involvement
  - Pulmonary veno-occlusive disease (evidence of pulmonary vascular congestion)
  - Pulmonary capillary hemangiomatosis
- Persistent PH of newborn.

- Group 2: Pulmonary hypertension due to left heart disease
  - Systolic dysfunction
  - Diastolic dysfunction
  - Valvular disease

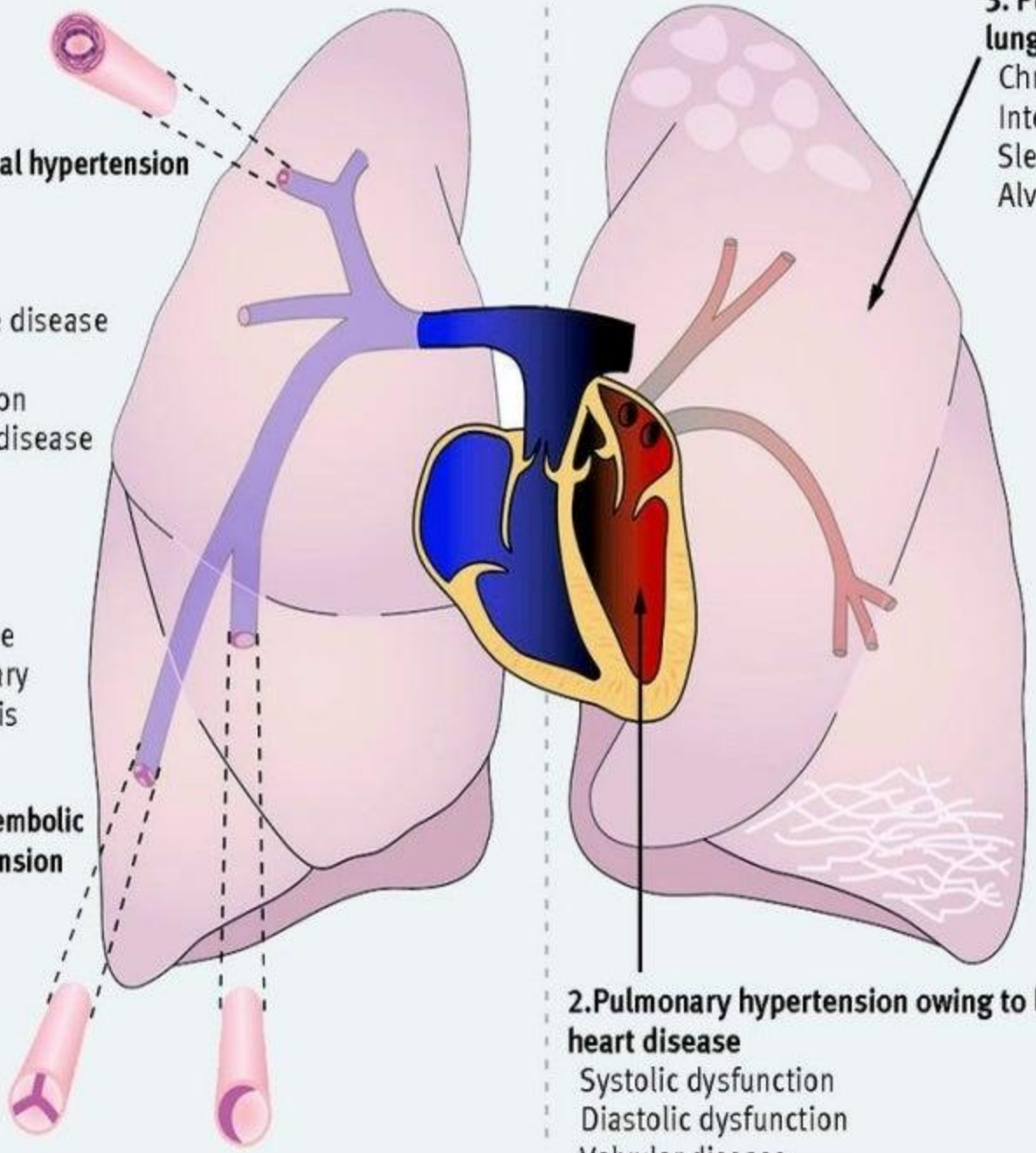
- Group 3: Pulmonary hypertension associated with lung disease and/or hypoxemia
  - Chronic obstructive lung disease
  - Interstitial lung disease
  - Sleep-disordered breathing
  - Alveolar hypoventilation disorders
  - Chronic exposure to high altitude
  - Developmental abnormalities

- Group 4: Pulmonary hypertension due to chronic thrombotic and/or embolic disease
  - Thromboembolic obstruction of proximal pulmonary arteries
  - Thromboembolic obstruction of distal pulmonary arteries

- Group 5: Miscellaneous
  - Sarcoidosis, histiocytosis X, lymphangiomyomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis, thyroid disorders, glycogen storage disease, Gaucher's disease,

Defined treatments

Optimal treatment not clear



1. Pulmonary arterial hypertension
- Idiopathic
- Heritable
- Drugs
- Connective tissue disease
- HIV
- Portal hypertension
- Congenital heart disease
- Schistosomiasis

1'
- Pulmonary veno-occlusive disease
- Pulmonary capillary haemaglomatosis

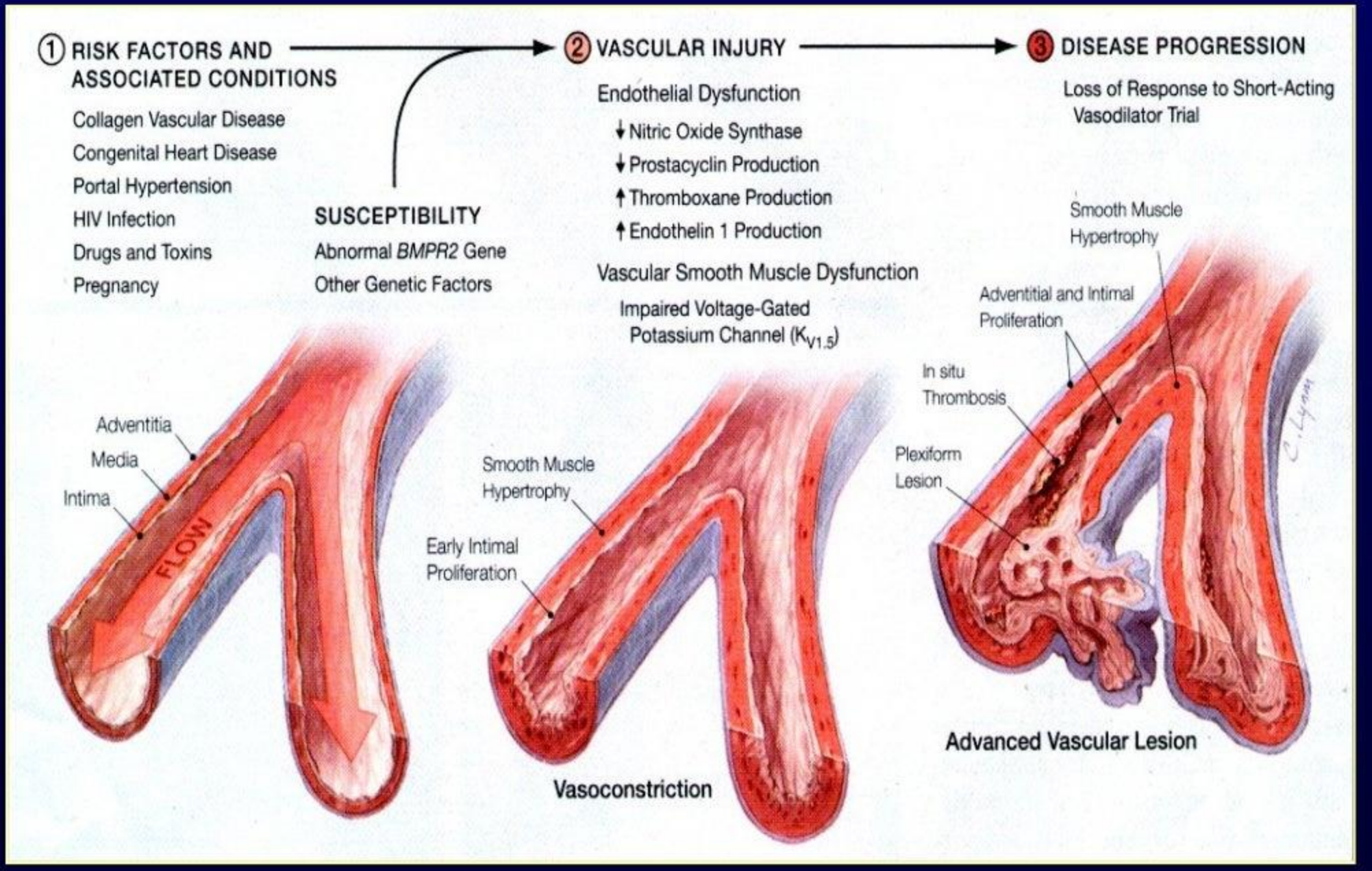
4. Chronic thromboembolic pulmonary hypertension
- Operable
- Inoperable

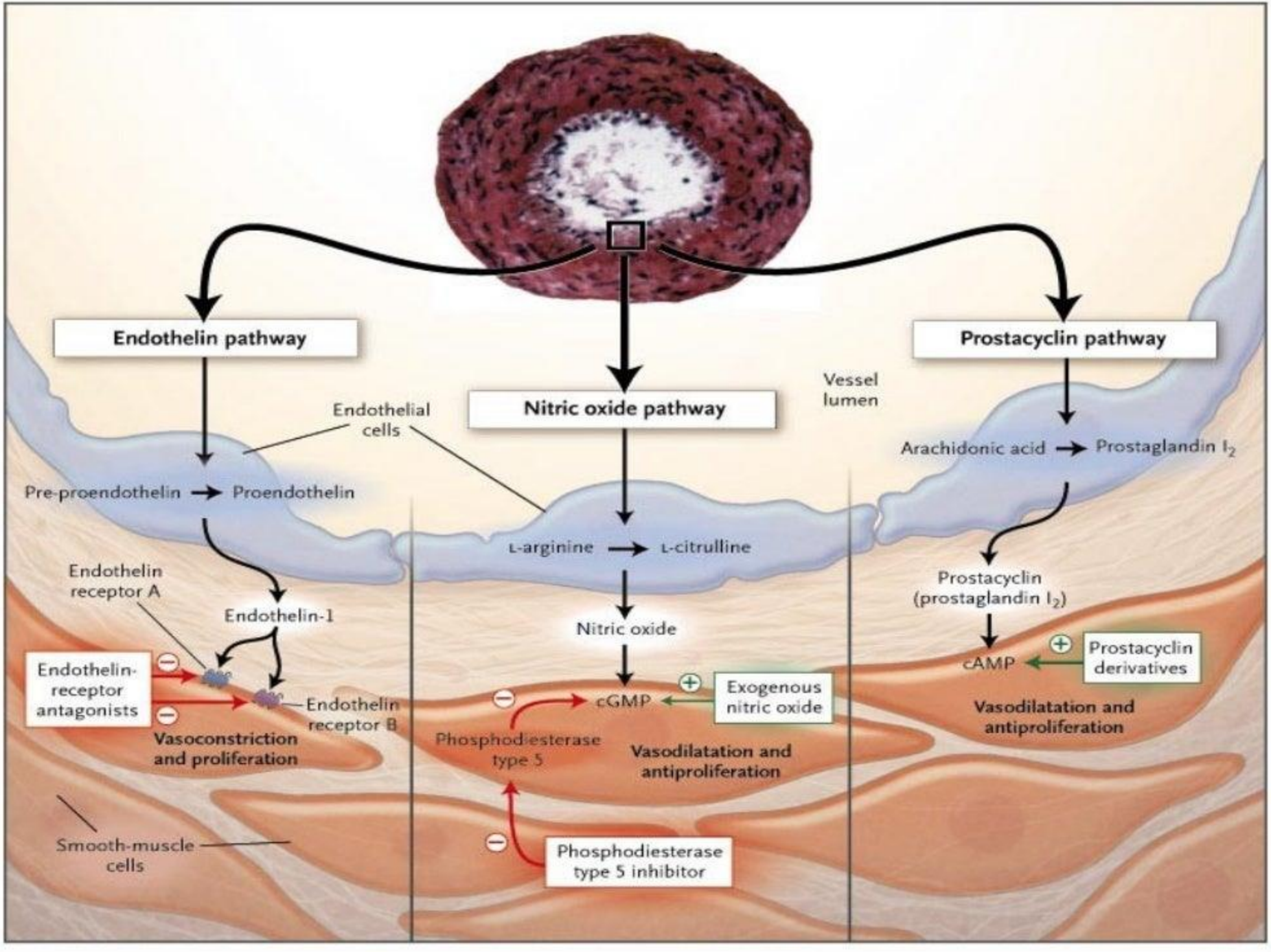
2.Pulmonary hypertension owing to left heart disease
- Systolic dysfunction
- Diastolic dysfunction
- Valvular disease

3. Pulmonary hypertension owing to lung disease/hypoxia
- Chronic obstructive pulmonary disease
- Interstitial lung disease
- Sleep disorder
- Alveolar hypoventilation

5. Multifactorial/unclear mechanisms
- Haematological
  - Chronic haematolytic anaemia
  - Myeloproliferative disease
  - Splenectomy
- Systemic disorders
  - Sarcoidosis
  - Langerhans cell histiocytosis
  - Lymphangioleiomyomatosis
  - Neurofibromatosis
  - Vasculitis
- Metabolic disorders
  - Glycogen storage disease
  - Gaucher's disease
  - Thyroid disorder
- Others
  - Tumour obstruction
  - Fibrosing mediastinitis
  - Chronic renal failure

Pathogenesis of Pulmonary ArterialHypertension




Endothelin pathway
Nitric oxide pathway
Prostacyclin pathway
Vessel lumen
Endothelial cells
Pre-proendothelin
Proendothelin
Endothelin receptor A
Endothelin-1
Endothelin-receptor antagonists
Endothelin receptor B
Vasoconstriction and proliferation
Smooth-muscle cells
L-arginine
L-citrulline
Nitric oxide
cGMP
Exogenous nitric oxide
Phosphodiesterase type 5
Vasodilatation and antiproliferation
Phosphodiesterase type 5 inhibitor
Arachidonic acid
Prostaglandin I_2
Prostacyclin (prostaglandin I_2)
cAMP
Prostacyclin derivatives
Vasodilatation and antiproliferation

Pathophysiology & Pathology – Group 1

- Exact mechanism – unknown.
- Multifactorial.

1)Excessive vasoconstriction -abnormal function or expression of potassium channels in the smooth muscle cells .

2) Endothelial dysfunction leads to chronically impaired production of vasodilator and Vasoconstrictors

(NO, prostacyclin, thromboxane A2 and endothelin-1)

3) Reduced plasma levels of other vasodilator and antiproliferative substances such as vasoactive intestinal peptide
4) In the adventitia there is increased production of extracellular matrix including collagen, elastin, fibronectin. Inflammatory cells and platelets (through the serotonin pathway)
5) Prothrombotic abnormalities have been demonstrated in PAH patients, and thrombi are present in both the small distal pulmonary arteries and the proximal elastic pulmonary arteries

1. Tunica media hypertrophy
2. Tunica intima proliferation
3. Fibrotic changes of tunica intima

   concentric eccentric

4. Tunica adventitial thickening with moderate perivascular infiltrates
5. Complex lesions

   Plexiform Dilated

6. Thrombotic lesions.

Pathophysiology & Pathology – Group 2

- Due to lt. heart diseases:
- Pulmonary venous hypertension-most common cause
- Usually due to left-sided heart disease (valvular, coronary or myocardial), →obstruction to blood flow downstream from the pulmonary veins.
- Reversibility is variable, dependent on lesion.

Table 2.—Causes of Pulmonary Venous Hypertension

Location	Condition
Aorta	Coarctation
	Supravalvular aortic stenosis
Left ventricle	Left ventricular failure of any cause
	Aortic stenosis
	Aortic regurgitation
	Congenital subaortic stenosis
	Hypertrophic cardiomyopathy
	Constrictive pericarditis
	Restrictive cardiomyopathy
	Dilated cardiomyopathy
	Mitral stenosis
	Mitral regurgitation
Left atrium	Ball-valve thrombus
	Myxoma
	Cor triatriatum
Pulmonary veins	Congenital pulmonary vein stenosis
	Mediastinitis
	Mediastinal fibrosis
	Mediastinal neoplasm

Pathophysiology & Pathology – Group 3

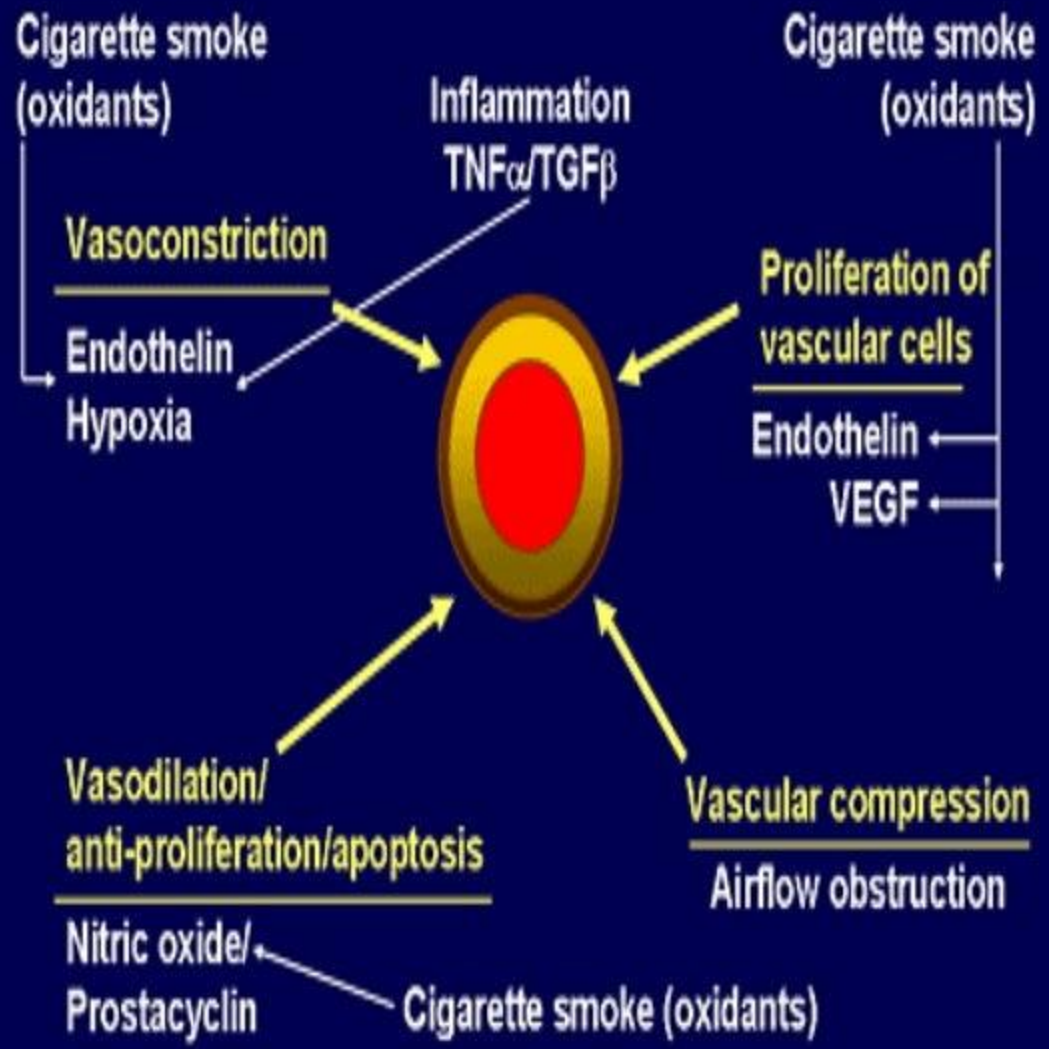
. PH due to lung diseases and/or hypoxia:

Multiple

1) hypoxic vasoconstriction,
2) mechanical stress of hyperinflated lungs,
3) loss of capillaries – emphysema, fibrosis
4) inflammation, and toxic effects of cigarette smoke.
5)endothelium-derived vasoconstrictor–vasodilator imbalance.

Hypoxia induced pulmonary vasoconstriction and anatomical destruction of the vascular bed due to high pulmonary resistance and ultimately RV failure.

Direct Toxic Effects of Cigarette Smoke



Wright JL et al. *Thorax*. 2005;60:605-609.

Pathophysiology & Pathology – Group 4

- CTEPH: non-resolution of acute embolic masses which later undergo fibrosis leading to mechanical obstruction of pulmonary arteries is the most important process.

Pathophysiology & Pathology – Group 5

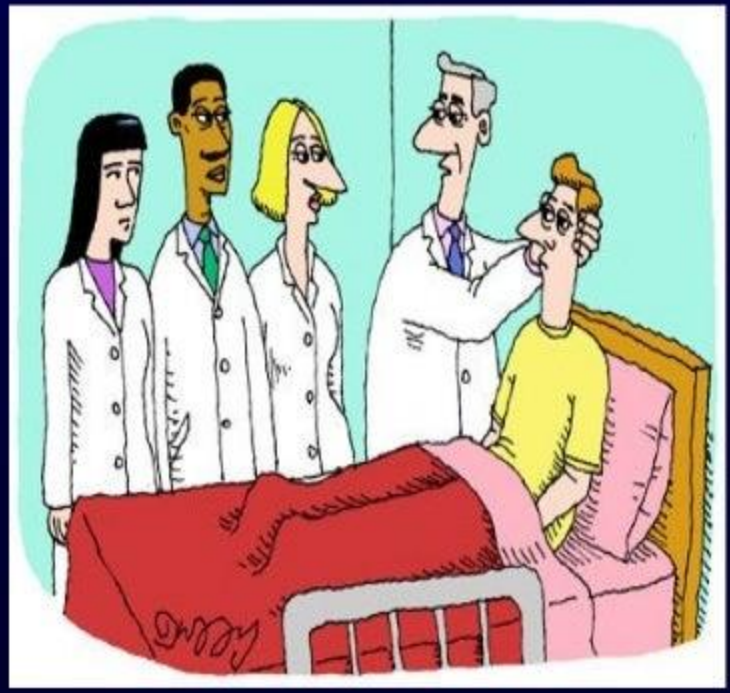
- PH with unclear and/or multifactorial mechanisms.

Drugs and toxins known to induce PAH

Definite	Possible
• Aminorex • Fenfluramine • Dexfenfluramine • Toxic rapeseed oil • Benfluorex	• Cocaine • Phenylpropanolamine • St John's Wort • Chemotherapeutic agents • Selective serotonin reuptake inhibitors • Pergolide
Likely	**Unlikely**
• Amphetamines • L-tryptophan • Methamphetamines	• Oral contraceptives • Oestrogen • Cigarette smoking

Reasons to Suspect PAH

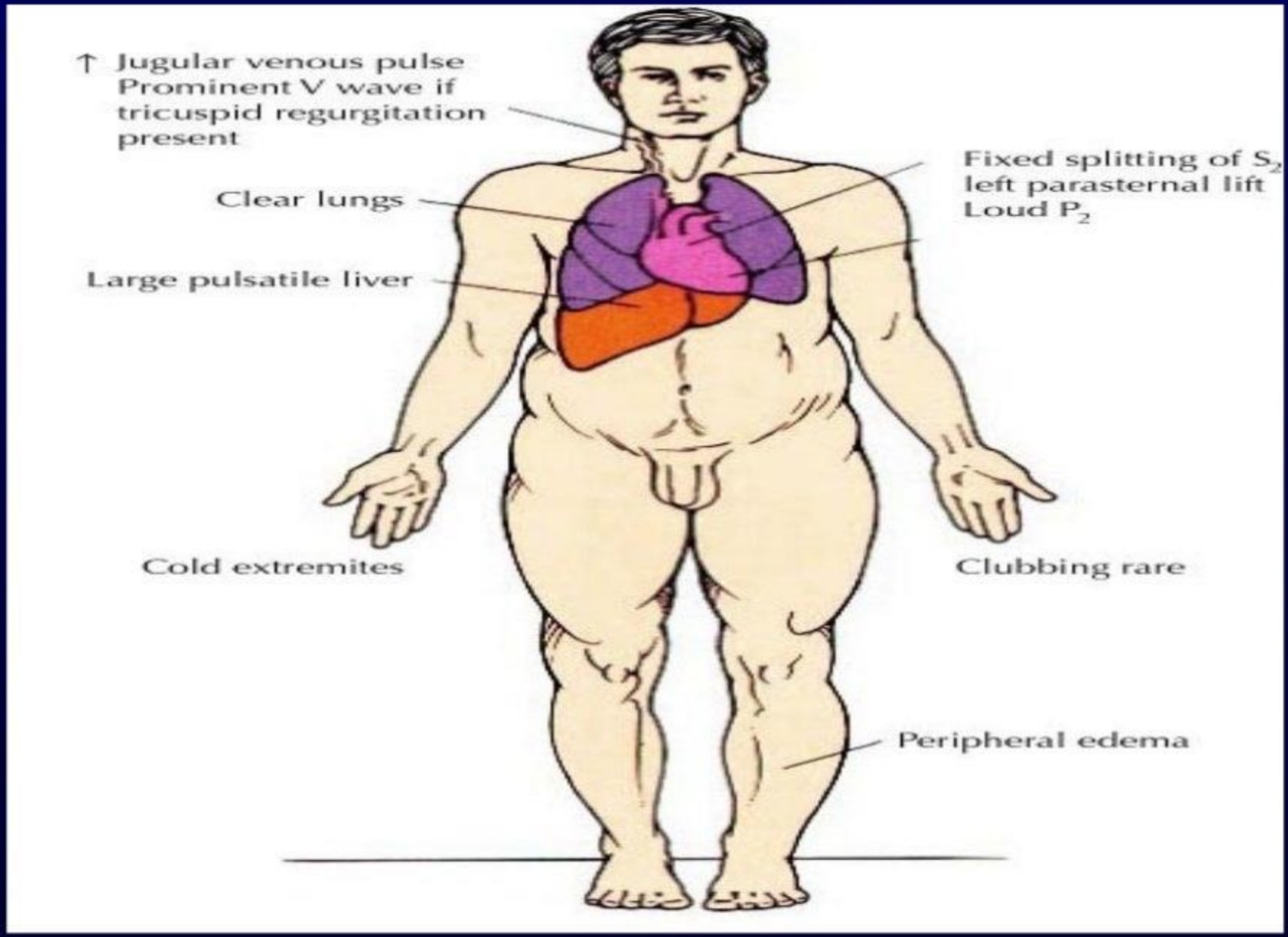
- Unexplained dyspnea despite multiple diagnostic tests
- Typical symptoms (look for Raynaud's)
- Comorbid conditons:
  - CREST, liver disease, HIV, sickle cell, OSA
  - Family history of PAH
  - History of stimulant/anorexigen use



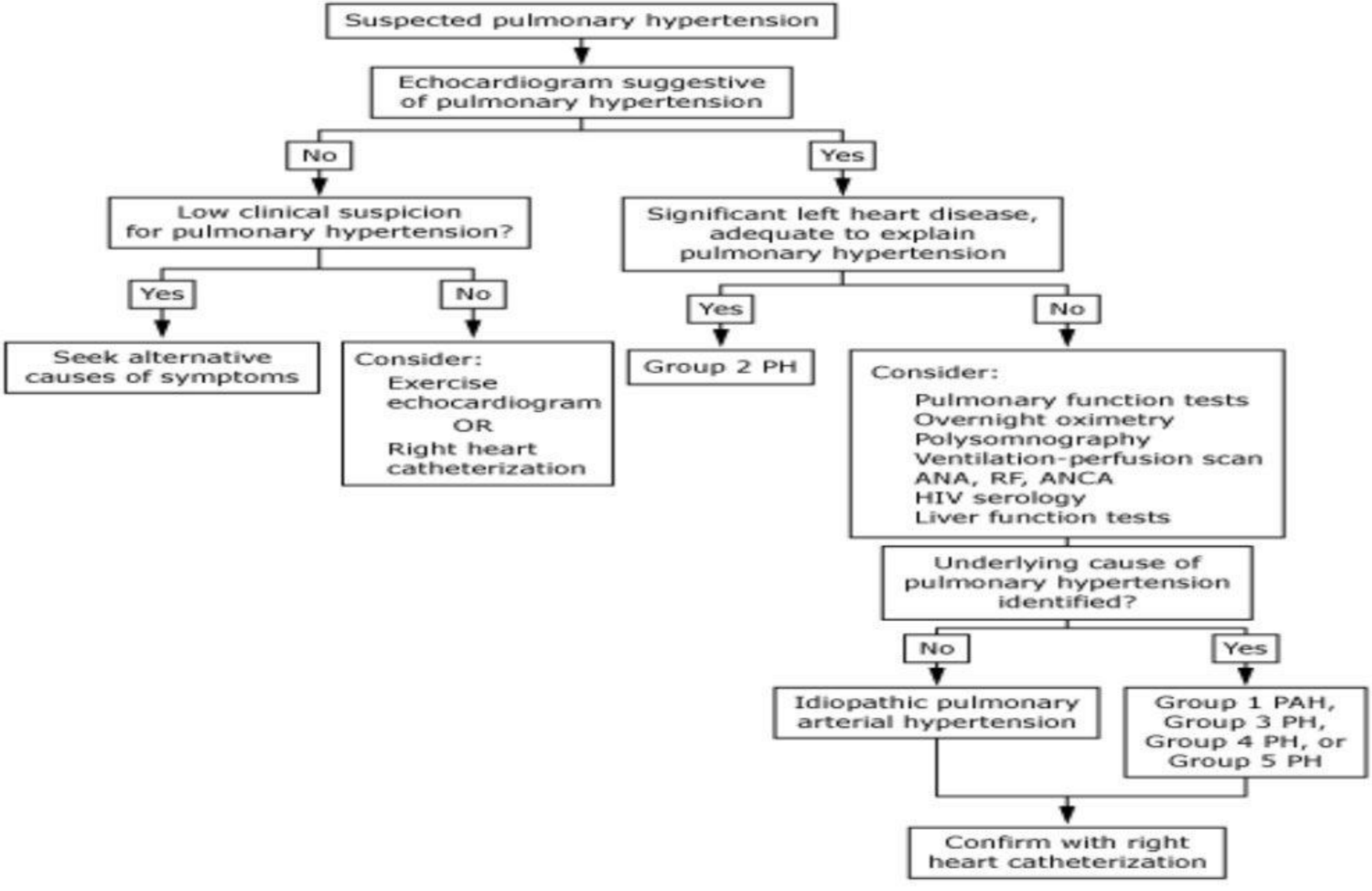
Symptoms of PAH

- Dyspnea 60%
- Fatigue 19%
- Near syncope/syncope 13%
- Chest pain 7%
- Palpitations 5%
- LE edema 3%
- Hoarseness of voice 2%
  (Ortners syndrome)

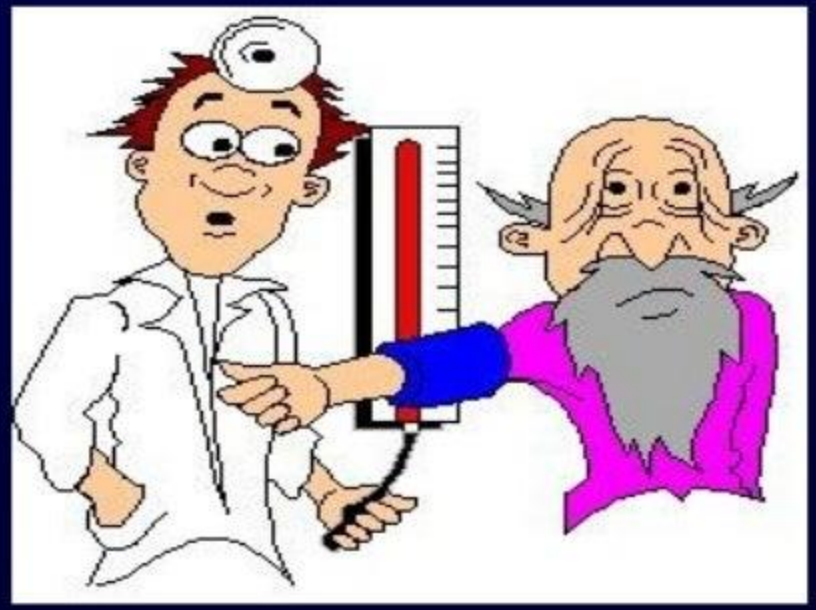
Physical Exam Findings in PH



Diagnostic Work-up of PAH



- Labs
  - Autoimmune serologies
  - Markers of liver synthetic function
  - HIV serologies when dictated by history



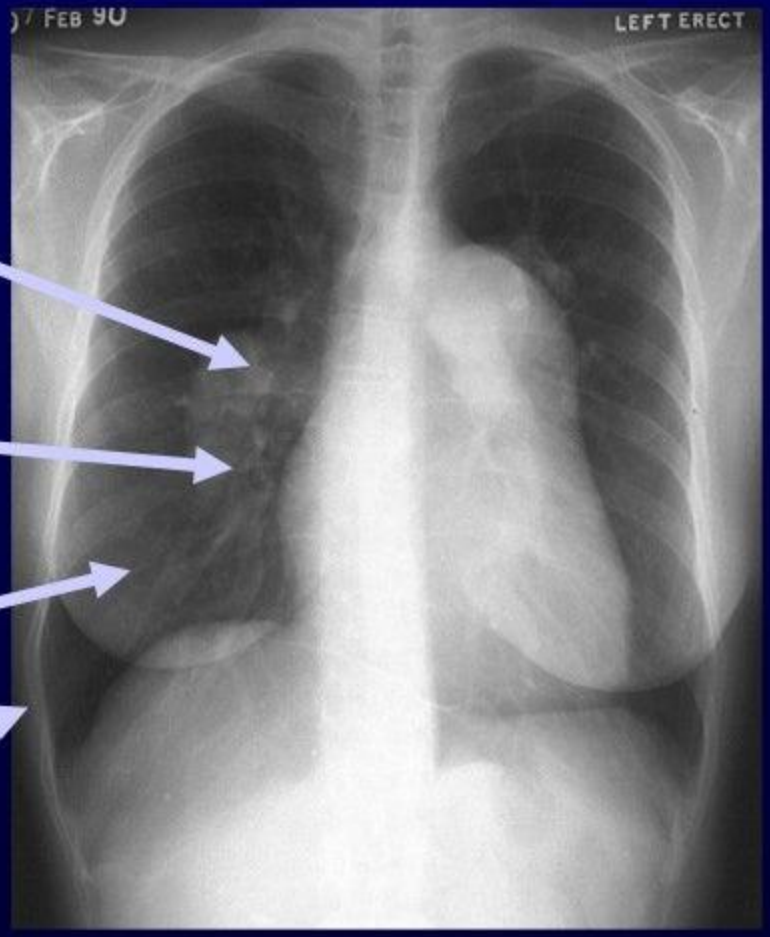
CXR in PH

Large central Pulmonary arteries

Right Ventricular Hypertrophy

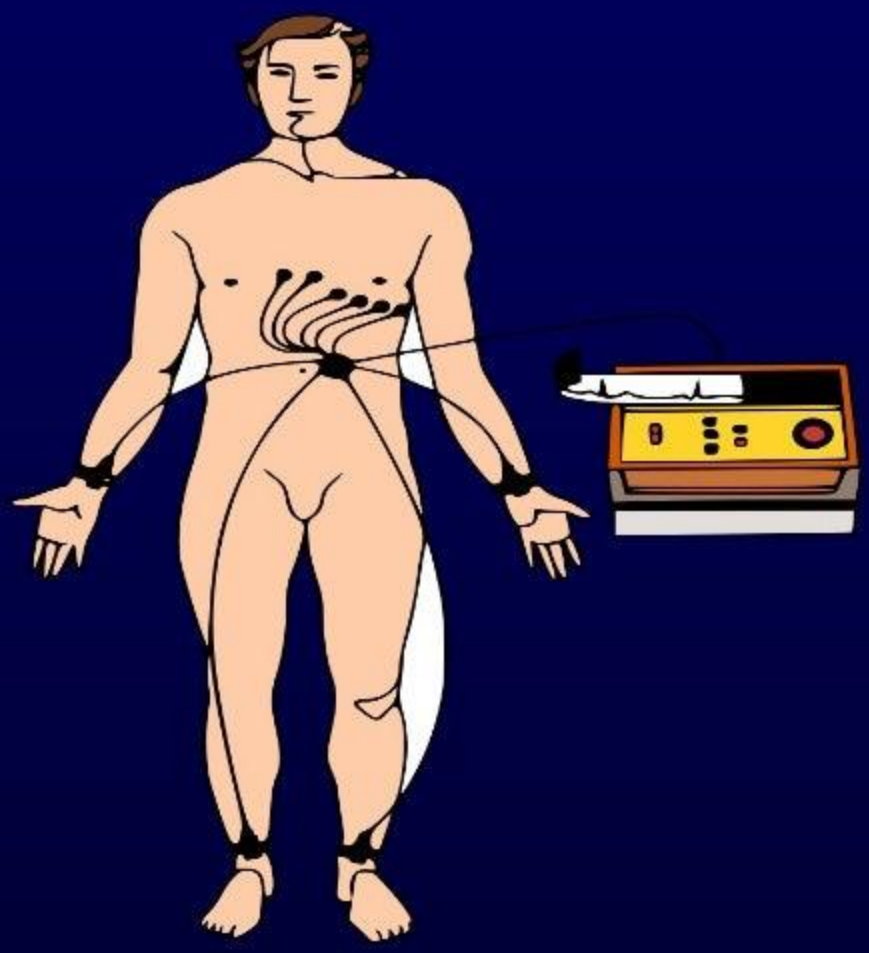
Rapid attenuation of pulmonary vessels

Clear Lung Fields



ECG in PH

- Right axis deviation
- An R wave/S wave ratio greater than one in lead V1
- Incomplete or complete right bundle branch block
- Increased P wave amplitude in lead II (P pulmonale) due to right atrial enlargement



- Echocardiogram
  - Order for screening when clinical suspicion exists
  - Order for standard interval screening in selected groups:
    - Family of those with IPAH or with known BMPR2 mutation
    - Scleroderma spectrum
    - Pre-liver transplant

Echocardiogram Findings

- TR
- Right atrial and ventricular hypertrophy
- Flattening of interventricular septum
- Small LV dimension
- Dilated PA
- Pericardial effusion
  - Poor prognostic sign
  - RA pressure so high it impedes normal drainage from pericardium
  - Do not drain, usually does not induce tamponade since RV under high-pressure and non-collapsible

Grading of pulmonary arterial hypertension*

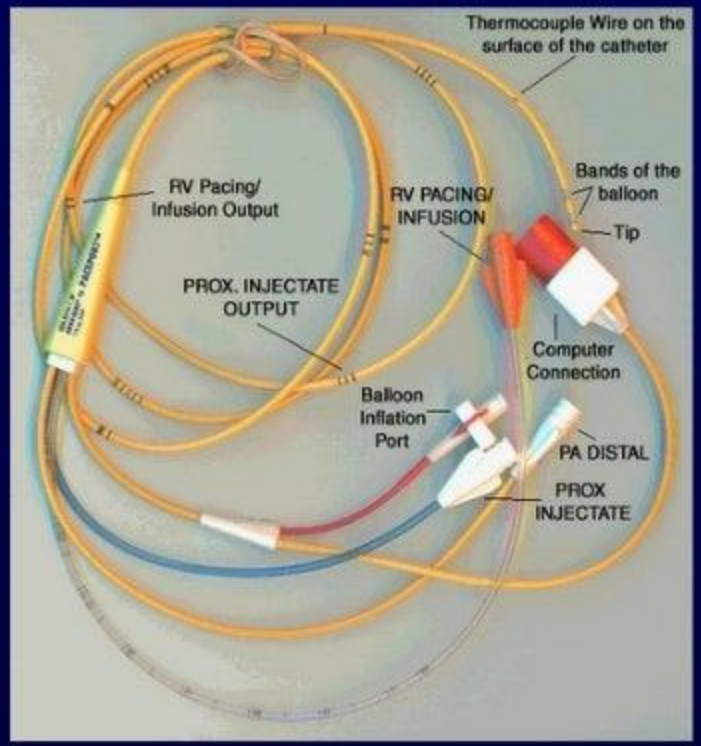
	Systolic	Diastolic	Mean
Grade 1 (Mild)	30-50	20-25	>30
Grade 2 (Moderate)	50-70	26-35	>40
Grade 3 (severe)	70-110	36-45	>50
Grade 4 (Systemic or supra systemic)	>110	46-55	>60

*Data from 100 patients of PAH and rheumatic heart disease. Quintile 1 & 2 (Grade 1) quntile 3 & 4 (Grade 2) quintile 5 (Grade 3) top 3%(Grade 4)

Right Heart Catheterization

- RA <6
- RV <30/6
- PA <30/12
- PCWP <12

- Pulmonary Vascular Resistance
- Cardiac Output by the Fick Equation



Calculation of pulmonary vascular resistance (PVR; Dyne-sec-cm^{-5}):

$$PVR = 80 \times \frac{[\text{Mean pulmonary artery pressure (mmHg)} - \text{left atrial pressure (mmHg)*}]}{\text{Pulmonary blood flow (L/min)•}}$$

Arteriovenous (AV) oxygen difference = (1.34) (Hgb concentration) (SaO_2 - SvO_2)

Fick cardiac output = $\frac{\text{Estimated oxygen consumption}}{10\ (\text{arteriovenous oxygen difference})}$

- Mean PAP pressure
  - At rest: >25mmHg
  - With exercise: >30mmHg
- Wedge Pressure: <15mmHg
- Pulmonary Vascular Resistance: > 240 dynes-cm-sec^{-5}

Always Rule out CTEPH

- Must be excluded in every case of PAH
- Potentially surgically remediable
- V/Q scan is preferred screening test
- CT pulmonary angiography

Vasoreactivity Testing During RHC

- Inhaled Nitric Oxide (NO) is a preferential pulmonary arterial vasodilator
- Positive if:
  - Mean PAP decreases at least 10 mmHg and to a value less than 40 mmHg
  - Associated increased or unchanged cardiac output
  - Minimally reduced or unchanged systemic blood pressure
- Only patients with Positive Vasoreactivity are given treatment trials with Calcium Channel Blockers!

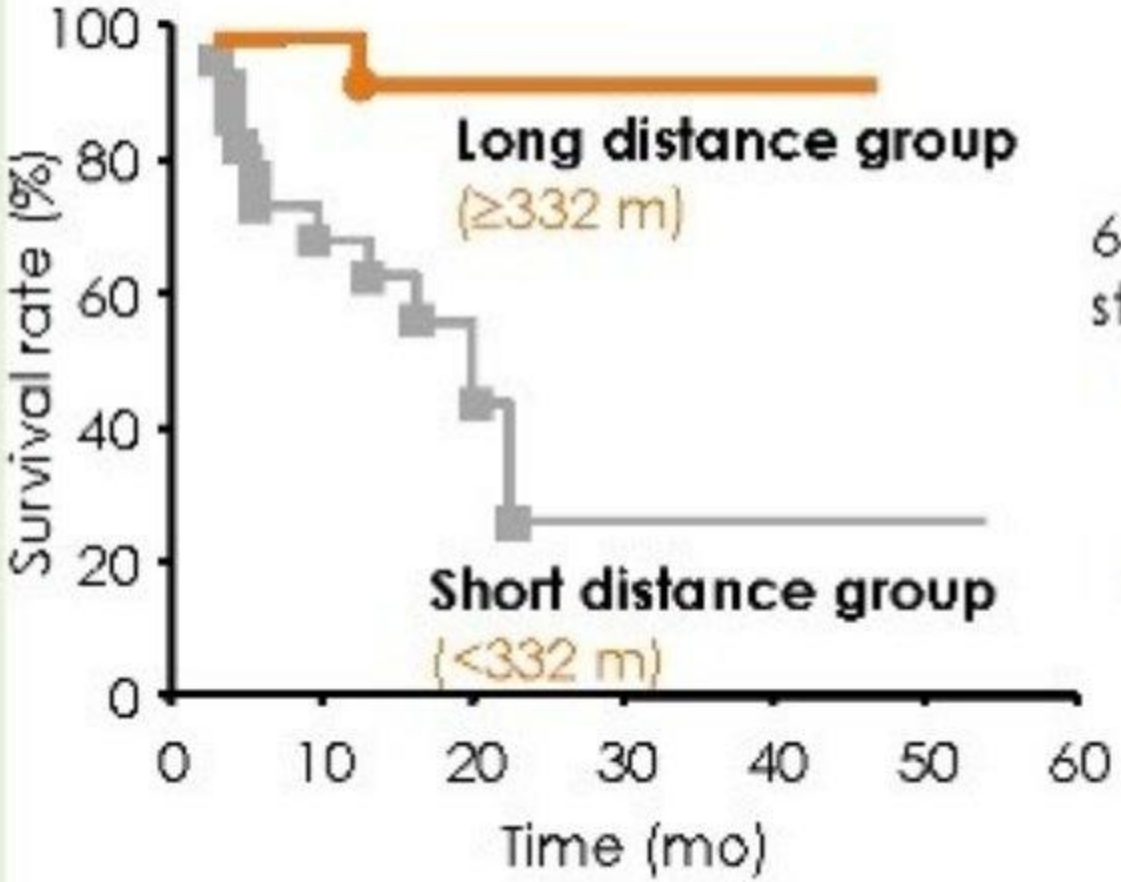
Why Treat PAH?

Survival & Prognosis of PAH

- Prognosis of the disease is very poor
- The median survival of patients with IPAH is 2.8 yrs
- Estimated survival rates are:
  - 68% at 1 year
  - 48% at 3 years
  - 34% at 5 years
- The estimated incidence of PAH among HIV-infected patients is 0.5% (1/200)
- PAH is found in 7-29% of patients with systemic sclerosis
- Median survival of patients who have scleroderma & PAH is approx 1 year

Clin Chest Med 2007; 28(1):1-22

Correlation of Six-minute-walk Test With Survival in PPH



6-minute-walk distance strongly predictive of survival

- <332 m: 20% 3-year survival
- >332 m: 92% 3-year survival

Miyamoto S et al. Am J Respir Crit Care Med. 2000;161:487-492.

REVEAL™

PAH risk score

WHO Group I subgroup	APAH-CTD	APAH-PoPH	FPAH	
	+1	+2	+2	
Demographics & comorbidities	Renal insufficiency		Males age >60 years	
	+1		+2	
NYHA/WHO functional class	I	III	IV	
	-2	+1	+2	
Vital signs	SBP <110 mmHg		HR >92 BPM	
	+1		+1	
6-minute walk test	≥440 m		<165 m	
	-1		+1	
BNP	<50 pg/mL		>180 pg/mL	
	-2		+1	
Echocardiogram	Pericardial effusion			
	+1			
Pulmonary function test	Percent predicted DLco ≥80		Percent predicted DLco ≤32	
	-1		+1	
Right heart catheterization	mRAP >20 mmHg within 1 year		PVR >32 Wood units	
	+1		+2	
			SUM OF ABOVE	
			+	6
			= RISK SCORE	

- Registry to Evaluate Early and Long-term PAH Disease Management
- **REVEAL Registry PAH risk score calculator.** Calculated risk scores can range from 0 (lowest risk) to 22 (highest risk).

Poor prognostic factors

- Age >45 years
- (WHO) functional class III or IV
- Failure to improve to a lower WHO functional class during treatment
- Echocardiographic findings of a pericardial effusion, large right atrial size, elevated right atrial pressure, or septal shift during diastole
- Decreased pulmonary arterial capacitance (ie, the stroke volume divided by the pulmonary arterial pulse pressure)
- Increased N-terminal pro-brain natriuretic peptide level (NT-pro-BNP)
- Prolonged QRS duration
- Hypocapnia
- Comorbid conditions (eg, COPD, diabetes)

Who do we treat for PAH?

- Treatment is based on functional status

New York Heart Association Functional Classification

Class 1: No symptoms with ordinary physical activity.

Class 2: Symptoms with ordinary activity. Slight limitation of activity.

Class 3: Symptoms with less than ordinary activity. Marked limitation of activity.

Class 4: Symptoms with any activity or even at rest.

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World Health Organization (WHO) functional classification for pulmonary hypertension

Class	WHO functional classification
I	Patients with pulmonary hypertension but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue or dyspnea, chest pain, or heart syncope.
II	Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in undue fatigue or dyspnea, chest pain, or heart syncope.
III	Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes undue fatigue or dyspnea, chest pain, or heart syncope.
IV	Patients with pulmonary hypertension resulting in inability to carry on any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may be present even at rest. Discomfort is increased by physical activity.

Data from: Rich, S. Primary pulmonary hypertension: executive summary. Evian, France. World Health Organization, 1998.

Graphic 62080 Version 1.0

How do we Treat Them?

- General measures:
  - Avoid pregnancy
    - Contraception imperative
    - Maternal mortality 30%
  - Immunizations for respiratory illnesses

    Influenza & pneumonia vaccinations
  - Minimize valsalva maneuvers—increase risk of syncope
    - Cough, constipation, heavy lifting, etc

Classes of therapy

- **MEDICAL**
  - Diuretics
  - Anti coagulants (IPAH)
  - Digoxin
  - Oxygen
  - PAH specific therapy
- **SURGICAL THERAPY**
  - Atrial septostomy
  - Lung transplantation

Diuretics

- Principally to treat edema from right heart failure
- May need to combine classes
  - -Thiazide and loop diuretics
- Careful to avoid too much pre-load reduction
- Patients often require large doses of diuretics

Anticoagulants

- Studies only show benefit in IPAH patients, based on improved survival.
- Other PAH groups not as clear, use in them considered expert opinion.
- Generally, keep INR 2.0-2.5.
- Thought to lessen in-situ thrombosis

Oxygen

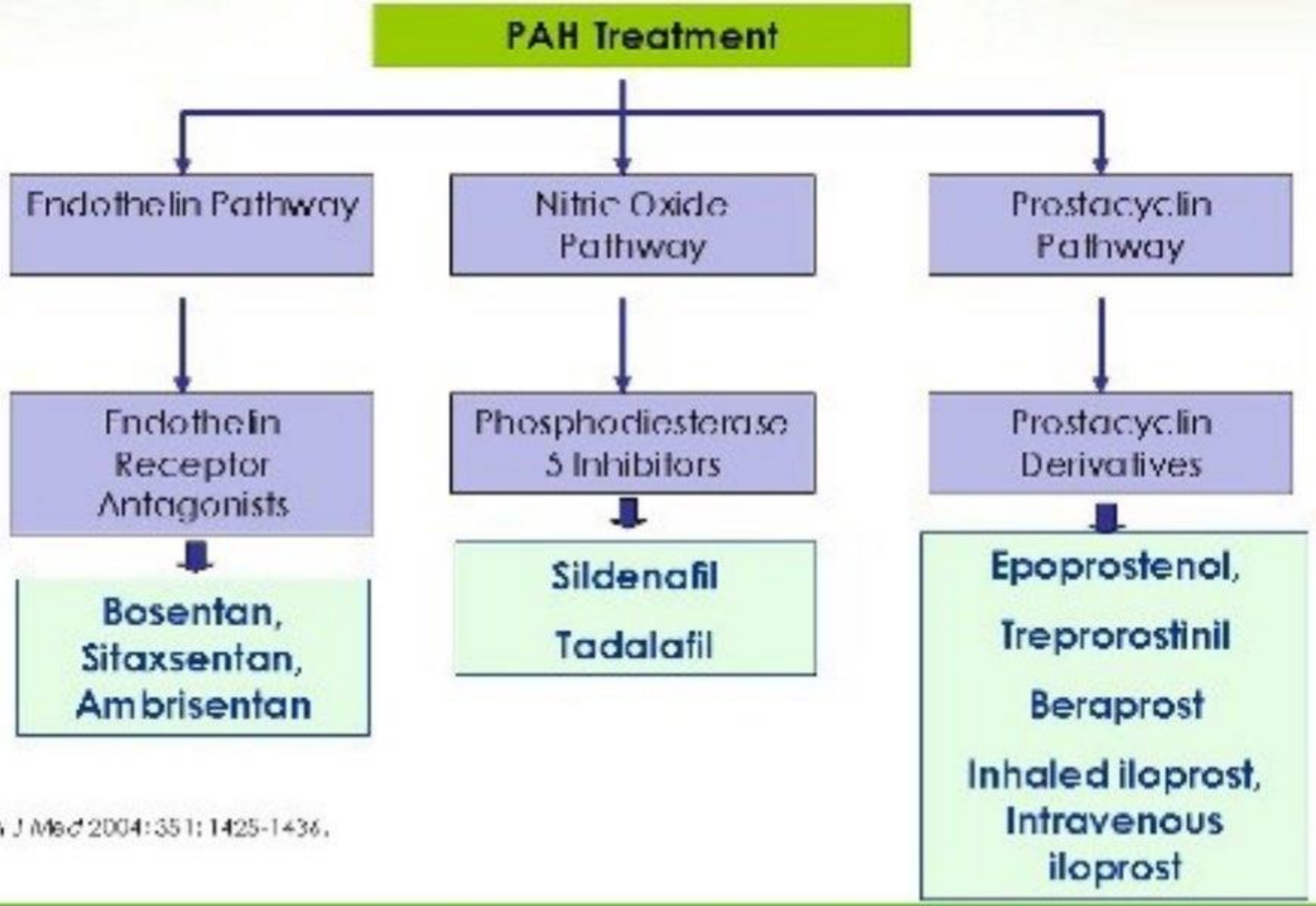
- Formal assessment of nocturnal and exertional oxygenation needs.
- Minimize added insult of hypoxic vasoconstriction
- Keep oxygen saturation ≥90%
  - May be impossible with large right to left shunt
- Exclude nocturnal desaturation
  - Overnight oximetry
- Rule out concomitant obstructive sleep apnea and hypoventilation syndromes

PAH-Specific Therapies

1) Calcium channel blockers
2) Endothelin receptor antagonists (ERAs)—
   Bosentan, Sitaxsentan, Ambrisentan

3) Phosphodiesterase (type 5) inhibitors (PDE 5-I)—
   Sildenafil, Tadalafil, Vardenafil.
4) Prostanoids—Epoprostenol, Treprostinil, Iloprost
5) Guanylate cyclase stimulant- Riociguat

Targeted Therapies for PAH



N Engl J Med 2004;351:1425-1436.

Calcium Channel Blockers

- Use only when demonstrated vasoreactivity in RHC (about 10% or less of patients)
- Diltiazem or nifedipine preferred.
- Titrate up to maximum tolerated dose.
- Systemic hypotension may prohibit use
- Only 50% of patients maintain response to CCB.
- Not in FC IV patients or severe right heart failure

Endothelin Receptor Antagonists (ETRA)

- Targets relative excess of endothelin-1 by blocking receptors on endothelium and vascular smooth muscle
- Bosentan, Ambrisentan, Sitaxentan, Macitentan
- Ambrisentan is ET-A selective.
- Both show improvement in 6MWD and time to clinical worsening.
- Monthly transaminase monitoring required for both
- Annual cost is high

- Potential for serious liver injury **(including very rare cases of unexplained hepatic cirrhosis after prolonged treatment)**

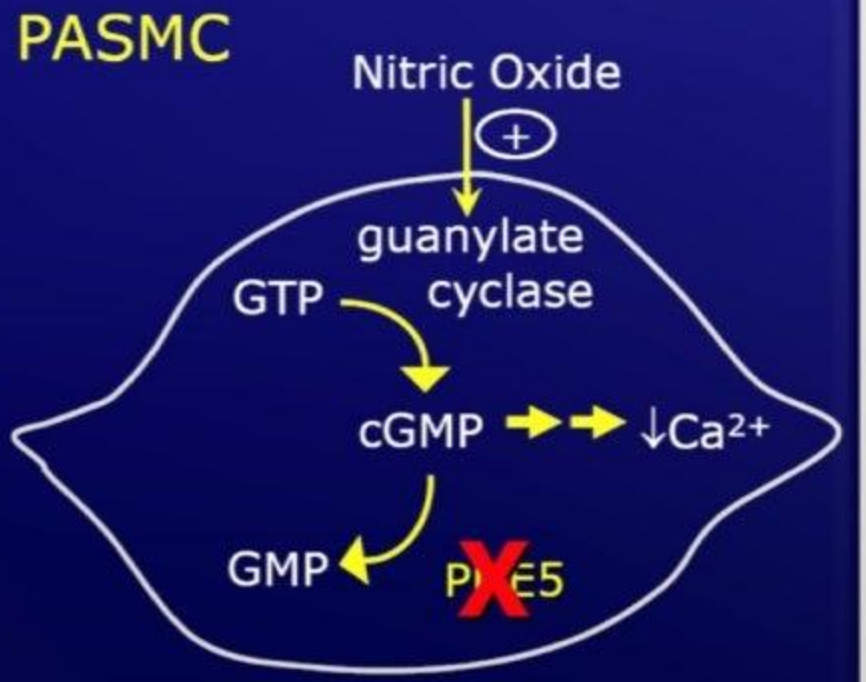
  - Oral dosing
    - Initiate at 62.5 mg BID for first 4 weeks
    - Increase to maintenance dose of 125 mg BID thereafter
    - Initiation and maintenance dose of 62.5 mg BID recommended for patients >12 years of age with body weight >40kg
  - No dose adjustment required in patients with renal impairment
  - No predetermined dose adjustments required for concomitant warfarin administration.

Ambrisentan

- 5 or 10 mg once daily
- Much less risk of transaminase elevation (about 1%), but monthly monitoring still required
- No dose adjustment of warfarin needed.

PDE-5 inhibitors

- Nitric oxide exerts effects thru cGMP pathway and is modulated by PDEs
- PDE-5 is located in walls of blood vessels
- Pulmonary vasculature predominantly has PDE-5



Sildenafil

- Safety
  - Side effects: headaches, epistaxis, and hypotension (transient)
  - Sudden hearing loss
  - Drug interaction with nitrates
  - FDA approved dose is 20 mg TID
  - Tadalafil 40mg OD
  - Vardenafil 5mg OD

Prostacyclin analogues

- Epoprostenol, treprostinil, iloprost
- Benefits
  - Vasodilation
  - Platelet inhibition
  - Anti-proliferative effects
  - Inotropic effects

Epoprostenol

- First PAH specific therapy available in the mid 1990's
- Lack of acute vasodilator response does not correlate well with epoprostenol unresponsiveness.
- Very short half life = 2 minutes
- Delivered via continuous infusion
- Cost about $100,000/year

Epoprostenol

- Side effects: headache, jaw pain, flushing, diarrhea, nausea and vomiting, flu-like symptoms, and anxiety/nervousness
- Complex daily preparation
- Individualized dosing
- Catheter complications
  - Dislodgement/malfunction
  - Catastrophic deterioration
  - Embolization
  - Infection (3% deaths)

Treprostinil (Remodulin)

- Continuous subcutaneous infusion or IV infusion
- Longer t1/2 = 4 hours
  - Less risk of rapid fatal deterioriation if infusion stops

Treprostinil

- Intravenous treprostinil
  - Hemodynamic improvements and 6MWD improvements
  - No site pain
  - Risk of catheter related bloodstream infection and embolic phenomenon
  - Recent concerns about increased gram-negative bloodstream infections.

Iloprost

- Inhaled prostacyclin
- Administered 6-9 times daily via special nebulizer
- Reported risk of morning syncope

Iloprost

- Improvements in 6MW, functional class and hemodynamics observed

  Olschewski H et al. *N Engl J Med* 2002;347:322-29

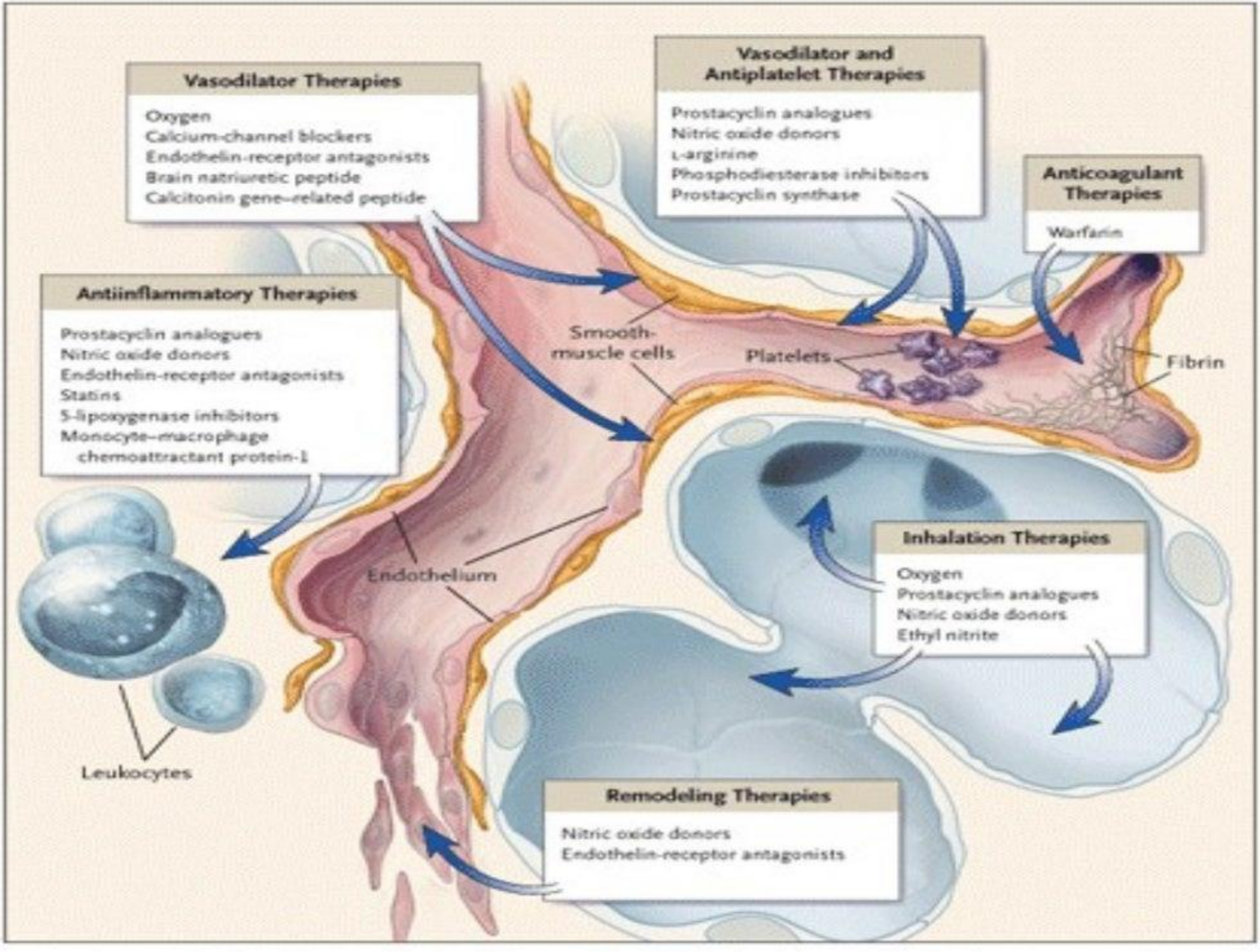
- Safety and side effects
  - Potential for increased hypotensive effect with antihypertensives
  - Increased risk of bleeding, especially with co-administration of anticoagulants
  - Flushing, increased cough, headache, insomnia
  - Nausea, vomiting, flu-like syndrome
  - Increased liver enzymes

Guanylate cyclase stimulant

- Stimulators of the nitric oxide receptor.
- Dual mode of action.
- They increase the sensitivity of sGC to endogenous nitric oxide (NO)
- Directly stimulate the receptor to mimic the action of NO.
- **Riociguat** is an oral sGC stimulant that has reported benefit in patients with inoperable and persistent chronic thromboembolic pulmonary hypertension (CTEPH;

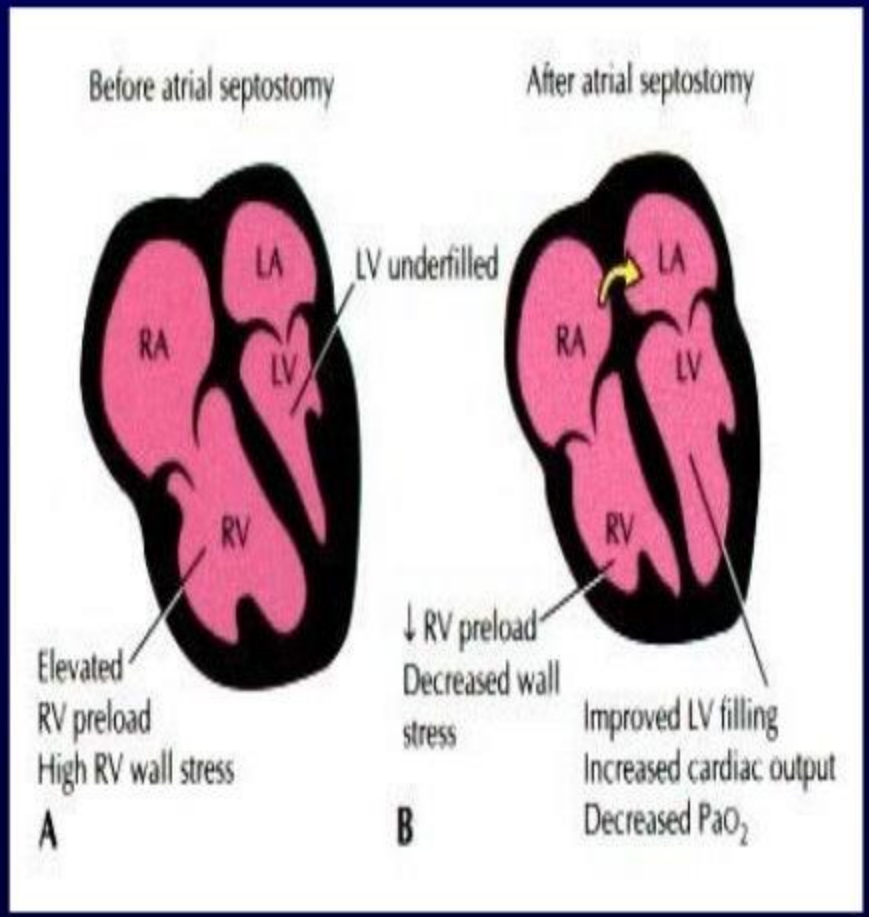
COMPASS Program

- COMPASS-2
  - Largest RCT in PAH ever
  - First morbidity and mortality trial
  - Assessing efficacy and safety of the combination of bosentan and sildenafil
- Comprehensive clinical trial program to lead the future management of PAH


Vasodilator Therapies
Oxygen
Calcium-channel blockers
Endothelin-receptor antagonists
Brain natriuretic peptide
Calcitonin gene–related peptide
Vasodilator and Antiplatelet Therapies
Prostacyclin analogues
Nitric oxide donors
L-arginine
Phosphodiesterase inhibitors
Prostacyclin synthase
Anticoagulant Therapies
Warfarin
Antiinflammatory Therapies
Prostacyclin analogues
Nitric oxide donors
Endothelin-receptor antagonists
Statins
5-lipoxygenase inhibitors
Monocyte–macrophage chemoattractant protein-1
Smooth-muscle cells
Platelets
Fibrin
Endothelium
Leukocytes
Inhalation Therapies
Oxygen
Prostacyclin analogues
Nitric oxide donors
Ethyl nitrite
Remodeling Therapies
Nitric oxide donors
Endothelin-receptor antagonists

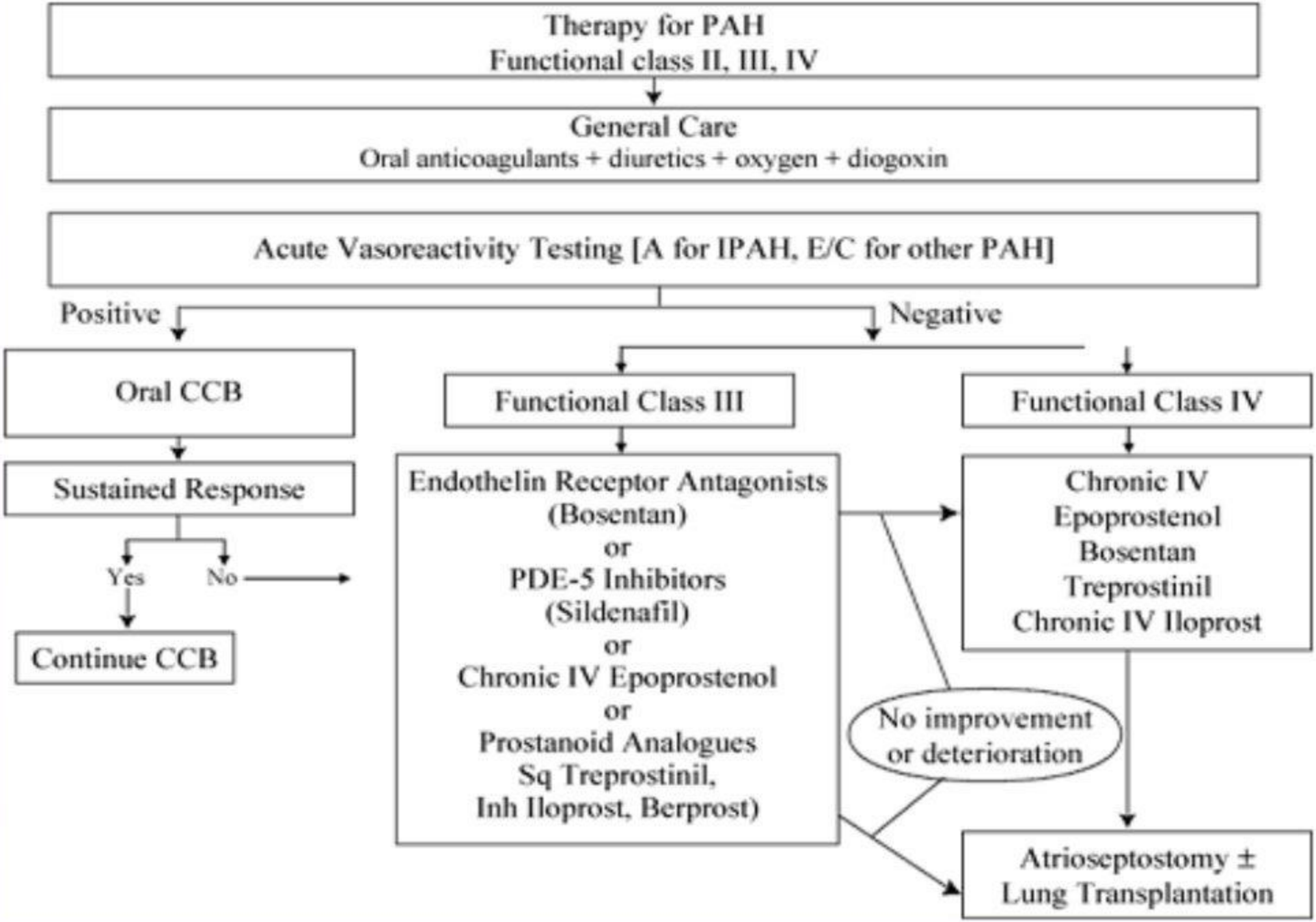
Failure of Medical Therapy: Consider Atrial Septostomy

- Improved left-sided filling
- Decreased right-sided pressures
- May serve as bridge to transplant



Failure of Medical Therapy: Indications for Lung Transplant

- New York Heart Association (NYHA) functional class III or IV
- Mean right atrial pressure >10 mmHg
- Mean pulmonary arterial pressure >50 mmHg
- Failure to improve functionally despite medical therapy
- Rapidly progressive disease


Therapy for PAH
Functional class II, III, IV
General Care
Oral anticoagulants + diuretics + oxygen + diogoxin
Acute Vasoreactivity Testing [A for IPAH, E/C for other PAH]
Positive
Negative
Oral CCB
Sustained Response
Yes
No
Continue CCB
Functional Class III
Endothelin Receptor Antagonists
(Bosentan)
or
PDE-5 Inhibitors
(Sildenafil)
or
Chronic IV Epoprostenol
or
Prostanoid Analogues
Sq Treprostinil,
Inh Iloprost, Berprost)
Functional Class IV
Chronic IV
Epoprostenol
Bosentan
Treprostinil
Chronic IV Iloprost
No improvement
or deterioration
Atrioseptostomy ±
Lung Transplantation

Following Response to Therapy

- Six minute walk test
- Echocardiogram
- Right heart catheterization
- BNP
- Functional class